PATENT SPECIFICATION

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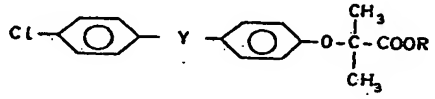
(19)

(54) SUBSTITUTED PHENOXY-α-METHYLPROPIONIC ACID DERIVATIVES AND A PROCESS FOR PRODUCING THE SAME

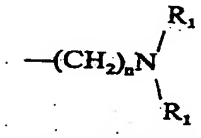
(71) We, FUNAI PHARMACEUTICAL INDUSTRIES, LTD., a Corporation organized and existing under the laws of Japan of No. 40 2-chome, Tsurigane-cho, Higashi-ku, Osáka, Japan, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to novel substituted phenoxy-α-methylpropionic acid derivatives and more particularly it relates to the compounds represented by the general formula (I):



(I)

wherein Y stands for $-CH_2-$, $-CH_2O-$, $-CH_2CH_2-$ or $-CH=CH-$, r stands for a hydrogen atom, an alkyl group having 1 to 6 carbon atoms or



n stands for an integer of 1 to 5 and R_1 stands for an alkyl group having 1 to 6 carbon atoms.

This invention further relates to a process for producing substituted phenoxy-α-methylpropionic acid derivatives.

Since the initial discovery that substituted phenoxy-α-methylpropionic acid derivatives were effective in the treatment of high concentrations of cholesterol in the blood serum, a number of other related compounds have been prepared as described in British Patent Specifications No. 860,303 and 898,596. The present inventors have found that the novel compounds of the formula (I) possess extremely high activity for reducing the level of cholesterol in the blood serum as well as low toxicity compared with the other related compounds.

It is, therefore, one object of this invention to provide novel compounds extremely effective in the treatment and prophylaxis of arteriosclerosis and hyperlipemia, such as severe cholesteremia.

It is another object of this invention to provide substituted phenoxy-α-methylpropionic acid derivatives having the formula (I).

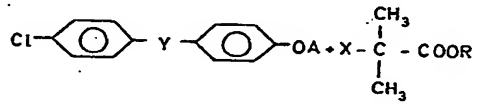
It is a further object of this invention to provide a process for

producing substituted phenoxy-α-methylpropionic acid derivatives represented by the formula (I).

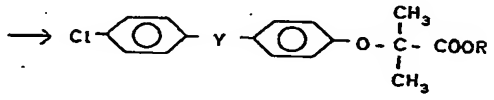
These and other objects, features and advantages of the present invention will become more fully apparent from the following description.

As suitable values of R in the formula (I), there may be mentioned, for example, a hydrogen atom, an alkyl group such as a methyl, ethyl, nor.-propyl, iso.-propyl, nor.-butyl, nor.-pentyl and nor.-hexyl group, and an N,N-di-alkylamino-alkyl group such as a dimethylaminoethyl and diethylaminoethyl group.

According to the present invention, the compounds having the formula (I) are produced as follows:



(II) (III)



(I)

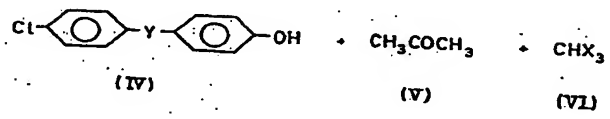
wherein A stands for a hydrogen atom or alkali or alkaline earth metal, X stands for a halogen atom, and Y and R are the same as heretofore defined.

That is, the present invention provides a process for producing substituted phenoxy-α-methylpropionic acid derivatives having the formula (I) which comprises reacting a *p*-substituted phenol or metallic salt thereof (II) with an α-halocarboxylic acid (III).

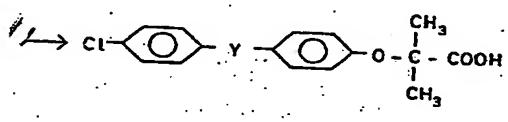
As suitable metallic salts (II) in the present process, there may be mentioned, for example, alkali metal salts such as potassium and sodium salts, and alkaline earth metal salts such as calcium and barium salts, while there may be mentioned halogen atoms such as bromine and chlorine as suitable values of X contained in the starting materials (III).

In carrying out the process of the present invention, starting materials (II) are reacted with starting materials (III) in such organic solvents as benzene, toluene, xylene and alcohols. The reaction may be conducted at room temperature, but the reaction is preferably conducted at an elevated temperature ranging from 60° to 140°C., thereby shortening the reaction time.

Alternatively, the compounds in which R stands for a hydrogen atom may be also produced as follows:



(IV) (V) (VI)



(I)

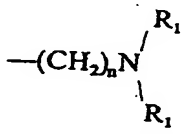
wherein Y is the same as heretofore defined.

This invention provides a process for producing a substituted phenoxy-α-methylpropionic acid (I) which comprises reacting a *p*-substituted phenol (IV) with acetone (V) and a trihalogenomethane (VI) in the presence of a base.

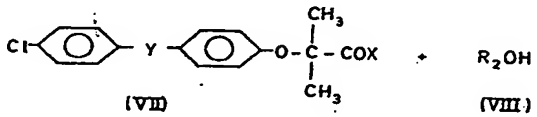
Suitable bases which may be used in this reaction include such strong bases as potassium hydroxide and sodium hydroxide.

In carrying out this process, *p*-substituted phenols (IV) are dissolved in acetone (V), to the resulting solution a trihalogenomethane (VI) such as chloroform is added dropwise under reflux conditions in the presence of a base, and then the reaction is continued during 5 to 8 hours, and there is obtained the desired compound (I).

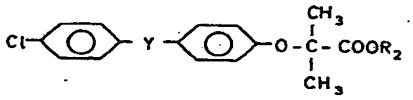
Moreover, the compound in which R stands for an alkyl group having 1 to 6 carbon atoms or



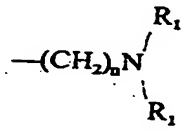
(n and R_1 are the same as heretofore defined), may be also produced as follows:



(VII) (VIII)



wherein R_2 stands for an alkyl group having 1 to 6 carbon atoms or



(n and R_1 are the same as heretofore defined), X stands for a hydroxyl group or a halogen, an acyloxy group or an alkoxy group except OR_2, and Y is the same as heretofore defined.

This invention provides a process for producing substituted phenoxy-α-methylpropionic acid derivatives (I) which comprises reacting an α-(*p*-substituted phenoxy)-α-methylpropionic acid or reactive derivative thereof (VII) with an alcohol (VIII).

Suitable reactive derivatives of an α-(4-substituted phenoxy)-α-methyl propionic acid include the acid halides, acid anhydrides, mixed acid anhydrides and esters, wherein preferred acid halides to be used are, for example, bromides or chlorides.

In carrying out this process, the reaction is, as a rule, preferably conducted in organic solvents, when using an acid halide as a starting material (VII). As suitable organic solvents, there may be mentioned, for example, basic solvents such as pyridine and quinoline, and neutral solvents such as benzene, toluene and xylene. The reaction may be conducted under conditions ranging from ice-cooling to room temperature, but the reaction is preferably carried out by heating to 40°—140°C., thereby the reaction time may be shortened.

When using the neutral solvents, the reaction may be conducted in the presence of a base such as tertiary amines or heterocyclic compounds containing nitrogen to afford good results.

When using the carboxylic acid (i.e. when X stands for a hydroxyl group) as a starting material (VII), a usual esterification method by dehydration is applied. That is, when the other starting material (VIII) is such a lower alcohol as methanol and ethanol, a starting material (VII) is reacted with excess starting material (VIII) under reflux conditions with or without such a catalyst as *p*-toluenesulfonic acid.

In the case where the starting material (VIII) is an N,N-di-alkylamino-alcohol, the reaction is conducted in organic solvent such as benzene, toluene and xylene under reflux conditions, while removing water formed from the reaction system using a water separator.

In the further case where an acid anhydride is used as the starting material (VII), whilst the reaction can be conducted in the absence of a solvent, the reaction proceeds more preferably when an organic solvent is used.

Suitable organic solvents which may be used in this reaction include heterocyclic compounds containing nitrogen such as pyridine and quinoline, basic solvents such as tertiary amines, and neutral solvents such as benzene, ether, dioxane, toluene and xylene.

The reaction is preferably conducted at room temperature, but increased temperatures ranging from 40° to 140°C. bring about a reduction in reaction time. When a neutral solvent is used, the solvent may be used as a mixed solvent with a base such as a tertiary amine and a heterocyclic compound containing nitrogen. Further, catalysts such as sulfuric acid and boron hydrides may be used.

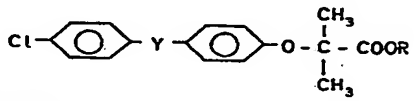
Of the compounds of the formula (I) obtained as described above, the compound in which R stands for an N,N-di-alkylamino-alkyl group may be converted to the corresponding organic or inorganic acid addition salts.

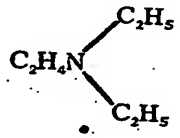
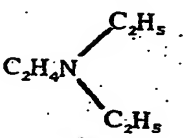
The pharmacological effects of the compounds of the formula (I) obtained according to the invention are as follows:

(1) Effects on the concentration of cholesterol in the blood serum.

The tests were carried out in 80 male SD (Sprague Dawley) strain rats, weighing approximately 160 g. There are 8 groups, that is, test compounds-treated and control group, either of which includes 10 animals. After fasting during sixteen hours prior to the administration, each test compound and control solution was administered orally. Eighteen hours after the last administration, the rats were killed by decapitation and the blood serum was obtained by a centrifugal procedure. Total cholesterol level in the blood serum was determined by a modification of the method of Zurkowski-Shibata. These results are given in Table 1. The dose is 100 mg/kg body weight at rat. The rate of inhibition of blood serum cholesterol level in rats is represented in the terms of per cent.

Table 1.



Test Compounds		Rate of inhibition of serum cholesterol level (%)
Y	R	
CH_2	C_2H_5	26.0
CH_2O	CH_3	36.0
CH_2	CH_3	24.0
CH_2O		18.7
CH=CH		16.9
CH_2	H	18.4
CH_2CH_2	H	14.7

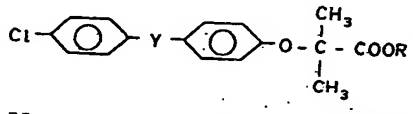
(2) Acute toxicity in mice.

To dd (Deutschland Denken.) strain male mice, weighting approximately 20 g., the test compounds were administered orally.

Each value of their LD50 was measured by the method of Lichfield-Wilcoxon [J. Pharmac. exp. Ther, *96*, 99 (1949)]. These results are given in Table 2.

Table 2.

The Compound



Y	R	LD50 (mg/kg)
CH_2	CH_3	2,950
CH_2O	C_2H_5	>8,000
CH_2O	CH_3	>8,000

(3) Comparison of pharmacological effects between known and present compounds:

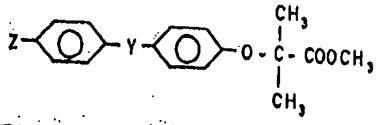
(a) Male SD strain rats weighting about 160 g. were divided into 5 groups consisting of ten in each. The test compounds which had been suspended in 0.5% CMC (Carboxymethyl cellulose), were administered to each of four groups in a dose of 100 mg/kg per day for seven days. To the control group, 0.5% CMC was administered in the same manner as described above. Water and feed were given freely all through the term, and body weight was measured at the administration of the test compounds.

After fasting for eighteen hours after completion of the last administration, the rats were killed by decapitation, their livers were immediately isolated and the blood was collected.

The blood samples were immediately centrifuged at 3000 r.p.m. for 15 minutes to separate serum. Cholesterol and triglyceride in the serum were determined by the modified Zurkowski-Shibata method and Banhander's method, respectively, and the rate of inhibition by each test compound were calculated. Serum GPT (Glutamic pyruvic transaminase) activity was measured by a transaminase reagent kit (Yatolon Co., Ltd.). The isolated liver was weighed immediately, and the ratio of liver weight to 100 gms of body weight was calculated.

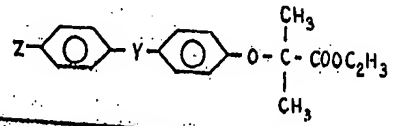
These results are given in Table 3 and Table 4.

TABLE 3



Test compounds	Z	Y	Serum Cholesterol mg/dl	Decrease (%)	Serum triglyceride mg/dl	Decrease (%)	Body weight gain a day g	Ratio (%)	Liver weight/ body weight (100g) g	Ratio (%)	Serum GPT activity Karmen Unit	Ratio (%)
Known Compounds	H	CH_2	64.4±2.8	23.0	37.3±2.1	30.5	8.2±0.6	97.6	3.6±0.08	112.5	22.2±1.2	100
	H	CH_2O	56.0±2.5	33.0	39.2±2.7	27.0	5.9±0.4	70.2	6.0±0.12	187.5	18.3±1.2	83.2
Present Compounds	Cl	CH_2	50.9±3.2	39.1	23.8±1.6	55.7	8.2±0.7	97.6	4.9±0.09	153.1	19.6±1.1	89.1
	Cl	CH_2O	45.1±3.1	46.1	19.2±1.9	64.2	8.5±1.1	101.2	3.4±0.06	106.3	20.8±0.8	94.5
Control			83.6±4.6	–	53.7±3.4	–	8.4±0.6	100	3.2±0.07	100	22.0±0.9	100

TABLE 4



Test compounds	Z	Y	Serum Cholesterol mg/dl	Decrease (%)	Serum triglyceride mg/dl	Decrease (%)	Body weight gain a day g	Ratio	Liver weight/ body weight (100g) g	Ratio	Serum GPT activity	
Known Compounds	H	CH					g		g			

(b) Male SD strain rats weighing about 190 g. were divided into 5 groups consisting of ten in each.

The test compounds which had been suspended in 0.5% CMC were administered to each of four groups in a dose of 50 mg/kg per day or 200 mg/kg per day for seven days. To the control group, 0.5% CMC was administered in the same manner as described above. Water and feed were given freely all through the term, and a body weight was measured at the administration of the test compounds.

After fasting for eighteen hours after completion of the last administration, rats were killed by decapitation, their livers were immediately isolated and the blood was collected. The blood samples were immediately centrifuged at 3000 r.p.m.for 15 minutes to separate serum. Cholesterol and triglyceride in the serum were determined by the modified Zurkowski method and Banhander's method, respectively, and the rate of inhibition by each test compound was calculated. Serum GPT activity was measured by a transaminase reagent kit (Yatolon Co., Ltd.). The isolated liver was weighed immediately, and the ratio of liver weight to 100 gms of body weight was calculated. 1 g. of the liver was extracted with chloroform-methanol (2:1 by volume) for 24 hours to obtain lipids, and then cholesterol and total lipids in the liver were determined by the above method and Holk's method, respectively, and the rate of inhibition by each test compound was calculated.

These results are given in Table 5.

TABLE 5–1

		Serum Cholesterol		Serum Triglyceride		Liver Total Cholesterol		Liver Total lipid	
		mg/dl	Decrease (%)	mg/dl	Decrease (%)	mg in Liver	Ratio (%)	mg in Liver	Ratio (%)
Ethyl 2-(*p*-Chlorophenoxy)-isobutyrate	50 mg/kg	46.4±3.4	17.1	38.2±2.0	34.8	39.5±1.4	-4.8		
	200 mg/kg	44.2±3.3	21.1	27.7±1.6	52.7	31.9±1.1	15.4	513.9±21.4	-18.5
Ethyl α-[*p*-(*p*'-chloro-benzyloxy)phenoxy]-α-methyl-propionate	50 mg/kg	49.7±4.3	11.2	35.3±2.6	39.8	33.8±1.5	103		
	200 mg/kg	40.3±1.5	28.0	29.8±3.3	49.1	32.8±2.3	13.0	247.9±9.1	42.8
Control		56.0±2.3	–	58.6±6.3	–	37.7±1.9	100	433.6±13.8	100

TABLE 5-2

		Body weight gain a day		Liver weight/ body weight (100g)		Serum GPT activity	
		g	Ratio (%)	g	Ratio (%)	Karmen Unit	Ratio (%)
Ethyl 2-(*p*-Chlorophenoxy)-isobutyrate	50 mg/kg	7.3±0.7	100	3.7±0.09	112.1	18.0±1.7	103.4
	200 mg/kg	6.6±0.4	90.4	4.7±0.13	142.4	21.3±1.9	122.4
Ethyl α-[*p*-(*p*'-chlorobenzyl-oxy)phenoxy]-α-methyl-propionate	50 mg/kg	7.4±0.5	101.4	3.4±0.06	103.0	18.3±0.9	105.2
	200 mg/kg	7.1±0.6	97.3	3.8±0.12	115.2	19.1±1.4	109.8
Control		7.3±0.4	100	3.3±0.05	100	17.4±1.7	100

As can be seen from Tables 3 to 5, it may conclude that the effectiveness of the present compound (I) are more valuable in the treatment and amelioration of angioscelerosis and lipid metabolism, compared with known compounds.

The following Examples are given by way of illustration only and are not to be construed as limiting unless otherwise specified.

Example 1.

12.0 g. of *p*-(*p*'-chlorobenzyloxy)phenol and 1.15 g. of metalic sodium were added to 100 ml. of xylene. The resulting mixture was refluxed with stirring for 3 hours. 12.2 g. of α-bromo-α-methylpropionic acid methyl ester was then added dropwise thereto for a period of approximately 20 minutes. The mixture obtained was then refluxed with stirring for 6 hours, followed by addition of water, thereby separating the organic layer. The water layer was extracted with ether. The combined crops of ethereal layer and the original organic layer were washed with water, dried, and the solvents were distilled off. Recrystallization of the resulting

residue from methanol afforded white crystals of α-[p(p'chlorobenzyloxy)phenoxyl-α-methylpropionic acid methyl ester having a melting point of 86° to 87°C.

Elemental Analysis: as $C_{18}H_{19}O_4Cl$

	C	H
Calculated (%)	64.58	5.72
Found (%)	64.47	5.57

Example 2.

6.6 g. of *p*-chloro-*p'*-hydroxystilbene and 0.7 g. of metallic sodium were added to 55 ml of xylene. The resulting mixture was refluxed with stirring for 4 hours. 5.5 g. of α-bromo-α-methylpropionic acid ethyl ester was added dropwise thereto with stirring under reflux for a period of approximatly 20 minutes. The mixture obtained was further refluxed for 5 hours. When the reaction was complete, water was added to the reaction mixture, and the organic layer was separated, and then treated in the same manner as described in Example 1. Recrystallization of the product from ethanol afforded α-[*p*-)*p'*-chlorostyryl)phenoxyl-α-methylpropionic acid ethyl ester having a melting point of 73° to 75°C.

Elemental Analysis: as $C_{20}H_{21}O_3Cl$

	C	H
Calculated (%)	69.70	6.09
Found (%)	69.88	6.00

Example 3.

9.4 g. of *p*-(*p'*-chlorobenzyloxy)phenol and 1.0 g. of metallic sodium were added to 30 ml. of xylene. The resulting mixture was refluxed with stirring for 3 hours. 8.8 g. of α-bromo-α-methylpropionic acid nor.-propyl ester was added dropwise thereto for a period of approximately 15 minutes. The mixture obtained was further refluxed for 6 hours. When the reaction was complete, the same procedure as described in Example 1 was performed. Recrystallization of the product from isopropyl alcohol afforded α-[*p*-(*p'*-chlorobenzyloxy)phenoxyl-α-methylpropionic acid nor.-propyl ester having a melting point of 40° to 42°C.

Elemental Analysis: as $C_{20}H_{23}O_4Cl$

	C	H
Calculated (%)	66.20	6.39
Found (%)	66.05	6.35

Example 4.

5.8 g. of *p*-(*p'*-chlorophenethyl)phenol and 0.57 g. of metallic sodium were added to 50 ml. of xylene. The resulting mixture was refluxed with stirring for 3 hours. 6.1 g. of α-bromo-α-methylpropionic acid methyl ester was added dropwise thereto for a period of approximately 15 minutes. The mixture obtained was further refluxed with stirring for 6 hours. When the reaction was complete, the same procedure as described in Example 1 was performed and there was obtained the product having a boiling point of 195°C./3 mmHg. Recrystallization thereof from methanol-water afforded α-[*p*-(*p'*-chlorophenethyl)phenoxyl-α-methylpropionic acid methyl ester having a melting point of 45° to 48°C.

Elemental Analysis: as $C_{19}H_{21}O_3Cl$

	C	H
Calculated (%)	68.56	6.36
Found (%)	68.84	6.49

Example 5.

To 100 ml. of anhydrous ethyl alcohol, 0.7 g. of metallic sodium was added to form the corresponding alcoholate, and then 6.6 g. of *p*-(*p'*-chlorobenzyl)phenol was added thereto and the resulting mixture was refluxed with stirring for 2.5 hours. 7.0 g. of α-bromo-α-methylpropionic acid ethyl ester was added dropwise thereto with stirring under reflux for a period of approximately 15 minutes. The mixture obtained was further refluxed with stirring for 4 hours. When the reaction was complete, the precipitate was filtered off and the filtrate was concentrated. To the resulting residue was added water and extracted with ether. The ethereal extract was then washed with water and the solvent thereof was distilled off. Distillation of the resulting residue under reduced pressure afforded α-[*p*-(*p'*-chlorobenzyl)phenoxy]-α-methylpropionic acid ethyl ester having a boiling point of 175° to 180°C./2 mmHg.

Elemental Analysis: as $C_{19}H_{21}O_3Cl$

	C	H
Calculated (%)	68.57	6.36
Found (%)	68.38	6.14

Example 6.

2.35 g. of *p*-(*p'*-chlorobenzyloxy)phenol and 1.1 g. of sodium hydroxide were added to 50 ml. of ethanol. The resulting mixture was refluxed with stirring for 2 hours. 2.0 g. of α-bromo-α-methylpropionic acid dissolved in 10 ml. of ethanol was then added dropwise thereto for a period of approximately 10 minutes. The mixture obtained was further refluxed with stirring for 3 hours. When the reaction was complete, the solvent was distilled off and the residue obtained was dissolved in water by application of heat to separate the insoluble material. After the filtrate was acidified with dilute hydrochloric acid, the material separating out therefrom was collected by filtration. Recrystallization thereof from isopropyl alcohol afforded white crystals of α-[*p*-(*p'*-chlorobenzyloxy)phenoxy]-α-methylpropionic acid having a melting point of 153° to 155°C.

Elemental Analysis: as $C_{17}H_{17}O_4Cl$

	C	H
Calculated (%)	63.65	5.34
Found (%)	63.43	5.11

Example 7.

2.4 g. of *p*-(*p'*-chlorobenzyloxy)phenol, 2.2 g. of α-bromo-α-methylpropionic acid ethyl ester and 1.3 g. of potassium carbonate were added to 50 ml. of acetone. The resulting mixture was refluxed with stirring for 15 hours. When the reaction was complete, the solvent was distilled off and the residue was treated with water and extracted with ether. The ethereal layer was washed with water and dried and the residue obtained was chromatographed on silica gel using chloroform as eluent. Recrylstallization of the product from isopropyl alcohol afforded α-[*p*-(*p'*-chlorobenzyloxy)phenoxy]-α-methylpropionic acid ethyl ester.

Elemental Analysis: as $C_{19}H_{21}O_4Cl$

	C	H
Calculated (%)	65.42	6.07
Found (%)	65.54	6.03

Example 8.

To the mixture of 5.4 g. of *p*-(*p'*-chlorobenzyl)phenol, 3.8 g. of sodium hydroxide and 22.1 g. of acetone, 3.8 g. of chloroform was added dropwise with stirring under reflux for a period of 15 minutes. The resulting mixture was further refluxed with stirring for 5 hours. When the reaction was complete, acetone was distilled off and the residue obtained was dissolved in water, acidified with dilute hydrochloric acid and extracted with ether. The ethereal layer was extracted with dilute sodium carbonate solution. The resulting alkaline extract was washed with ether and acidified with dilute hydrochloric acid and the crystals separating out therefrom were collected by filtration. Recrystallization from cyclohexane afforded white crystals of α-[*p*-(*p'*-chlorobenzyl)phenoxy]-α-methylpropionic acid having a melting point of 79° to 81°C.

Elemental Analysis: as $C_{17}H_{17}O_3Cl$

	C	H
Calculated (%)	67.00	5.62
Found (%)	67.08	5.66

Example 9.

To the mixture of 4.7 g. of *p*-(*p'*-chlorobenzyloxy)phenol, 3.8 g. of sodium hydroxide and 20.0 g. of acetone, 3.2 g. of chloroform was added dropwise with stirring under reflux for a period of approximately 15 minutes. Thereafter, the same procedure as described in Example 8 was performed. Recrystallization of the product from isopropyl alcohol afforded white crystals of α-[*p*-(*p'*-chlorobenzyloxy)phenoxy]-α-methylpropionic acid having a melting point of 153° to 155°C.

Elemental Analysis: as $C_{17}H_{17}O_4Cl$

	C	H
Calculated (%)	63.65	5.34
Found (%)	63.43	5.11

Example 10.

To the mixture of 3.0 g. of *p*-(*p'*-chlorophenethyl)phenol, 3.0 g. of sodium hydroxide and 12.5 g. of acetone, 2.5 g. of chloroform was added dropwise with stirring under reflux for a period of approximately 15 minutes. Thereafter, the same procedure as described in Example 8 was performed. Recrystallization of the product from cyclohexane afforded white crystals of α-[*p*-(*p'*-chlorophenethyl)phenoxy]-α-methylpropionic acid having a melting of 117° to 120°C.

Elemental Analysis: as $C_{18}H_{19}O_3Cl$

	C	H
Calculated (%)	67.82	6.09
Found (%)	67.99	6.19

Example 11.

To the mixture of 3.6 g. of *p*-chloro-*p'*-hydroxystilbene, 3.0 g. of sodium hydroxide and 15 ml. of acetone, 2.5 g. of chloroform was added dropwise with stirring under reflux for a period of approximately 15 minutes. Thereafter, the same procedure as described in Example 8 was performed. Recrystallization of the product from acetone afforded white crystals of α-[*p*-(*p'*-chlorostyryl)phenoxy]-α-methylpropionic acid.

Elemental Analysis: as $C_{18}H_{17}O_3Cl$

	C	H
Calculated (%)	68.25	5.41
Found (%)	68.34	5.44

Example 12.

To the mixture of 7.2 g of *p*-(*p'*-chlorobenzyloxy)phenol, 8.3 g. of potassium hydroxide and 31 g. of acetone, 5.0 g. of chloroform was added dropwise with stirring under reflux for approximately 20 minutes. Thereafter, the same procedure as described in Example 8 was performed. Recrystalization of the product from isopropyl alcohol afforded white crystals of α-[*p*-(*p'*-chlorobenzyloxy)phenoxy]-α-methylpropionic acid. The melting point and the infrared spectrum of the product were identical to those of an authentic sample obtained in Example 8.

Example 13.

To the mixture of 7.2 g. of *p*-(*p'*-chlorobenzyloxy)phenol, 8.3 g. of potassium hydroxide and 31 g. of acetone, 10.1 g. of bromoform was added dropwise with stirring under reflux for a period of approximately 15 minutes. Thereafter, the same procedure as described in Example 8 was performed. Recrystallization of the product from isopropyl alcohol afforded white crystals of α-[*p*-(*p'*-chlorobenzyloxy)phenoxy]-α-methylpropionic acid. The melting point and the infrared spectrum of the product were identical to those of an authentic sample obtained in Example 9.

Example 14.

3.1 g. of α-[*p*-(*p'*-chlorobenzyl)phenoxy]-α-methylpropionic acid was dissolved in 40 ml. of anhydrous ethanol and 0.2 g. of *p*-toluenesulfonic acid was added thereto and the mixture was then refluxed for 3 hours. When the reaction was complete, solvent was distilled off and the residue obtained was dissolved in ether and washed with water and the solvent was distilled off. Distillation of the residual thus obtained under reduced pressure afforded a clear liquid of α-[*p*-(*p'*-chlorobenzyl)phenozy]-α-methylpropionic acid ethyl ester having a boiling point of 185° to 186°C./2 mmHg.

Elemental Analysis: as $C_{19}H_{21}O_3Cl$

	C	H
Calculated (%)	68.57	6.36
Found (%)	68.38	6.53

Example 15.

4.0 g. of α-[*p*-(*p'*-chlorobenzyloxy)phenoxy]-α-methylpropionic acid was dissolved in 40 ml. of anhydrous methanol and 0.2 g. of *p*-toluenesulfonic acid was added thereto. The resulting solution was refluxed for 4 hours. When the reaction was complete, methanol was distilled off and the residue obtained was treated in the same manner as described in Example 14. Recrystalization thereof from methanol afforded white crystals of α-[*p*-(*p'*-chlorobenzyloxy)phenoxy]-α-methylpropionic acid methyl ester having a melting point of 86° to 87°C.

Elemental Analysis: as $C_{18}H_{19}O_4Cl$

	C	H
Calculated (%)	64.58	5.72
Found (%)	64.47	5.57

Example 16.

3.2 g. of α-[p-(p'-chlorostyryl)phenoxy]-α-methylpropionic acid and 1.2 g. of 2-(N,N-diethylamino)ethanol were added to 40 ml. of xylene. The resulting solution was then refluxed with stirring in a flask fitted with a water separator for 6 hours. The reaction mixture was poured into water and extracted with ether. Said extract solution was washed with dilute sodium carbonate solution and then water and dried. Thereafter, dry hydrochloric acid gas was passed into the solution to separate out crystals, which were collected by filtration. Recrystallization thereof from ethanol afforded white crystals of α-[p-(p'-chlorostyryl)phenoxy]-α-methylpropionic acid 2-(N,N-diethylamino)ethyl ester hydrochloride having a melting point of 174° to 176.5°C.

Elemental Analysis: as $C_{24}N_{31}O_3NCl$

	C	H	N
Calculated (%)	63.86	6.70	3.10
Found (%)	63.90	7.00	2.92

Example 17.

1.6 g. of α-[p-(p'-chlorobenzyloxy)phenoxy]-α-methylpropionic acid and 0.5 g. of 2-(N,N-dimethylamino)ethanol were added to 50 ml. of xylene. The resulting solution was refluxed with stirring in a flask fitted with a water separator. After the reaction was complete, the same procedure as described in Example 16 was performed. Recrystallization of the product from isopropyl alcohol afforded white crystals of α-[p-(p'-chlorobenzyloxy)phenoxy]-α-methylpropionic acid 2-(N,N-dimethylamino)ethyl ester hydrochloride having a melting point of 101° to 103°C.

Elemental Analysis: as $C_{21}H_{27}O_4Cl_2N$

	C	H	N
Calculated (%)	58.88	6.35	3.27
Found (%)	58.10	6.41	2.97

Example 18.

6.0 g. of α-[p-(p'-chlorostyryl)phenoxy]-α-methylpropionic acid chloride was dissolved in 40 ml. of benzene and to the resulting solution was added dropwise 1.6 g. of 2(N,N-dimethylamino)ethanol dissolved in 20 ml. of benzene with stirring at room temperature for a period of approximately 15 minutes. The reaction mixture was then further refluxed for 1.5 hours. After the reaction was complete, the mixture was cooled to room temperature and the crystals separating out therefrom were collected by filtration and dried. Recrystallization thereof from isopropyl alcohol afforded white crystals of α-[p-(p'-chlorostyryl)phenoxy]-α-methylpropionic acid 2-(N,N-dimethylamino)ethyl ester hydrochloride having a melting point of 188° to 191°C.

Elemental Analysis: as $C_{22}H_{27}O_3Cl_2N$

	C	H	N
Calculated (%)	62.27	6.41	3.30
Found (%)	62.04	6.40	3.12

Example 19.

(1) 5.0 g. of α-[p-(p'-chlorobenzyloxy)phenoxy]-α-methylpropionic acid and 2.0 g. of N,N-dicyclohexylcarbodiimide were added to 80 ml. of acetonitrile. The resulting solution was stirred at room temperature for 2 hours and allowed to stand overnight. N,N-dicyclohexylurea separating out therefrom was filtered off and the filtrate was evaporated under reduced pressure. Recrystallization of the residue from ether-ligroin mixed solvent afforded white crystals of α-[p-(p'-chlorobenzyloxy)phenoxy]-α-methylpropionic acid anhydride having a melting point of 116° to 117°C.

Elemental Analysis: as $C_{34}H_{32}O_7Cl_2$

	C	H
Calculated (%)	65.49	5.17
Found (%)	65.66	5.23

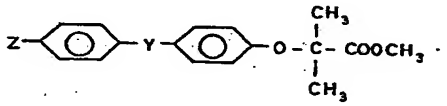
(2) 1.0 g. of α-[p-(p'-chlorobenzyloxy)phenoxy]-α-methylpropionic acid anhydride and 1.2 g. of nor.-propanol were dissolved in 3 ml. of pyridine. The resulting solution was heated to 80° to 95°C., which temperature was maintained for 4 hours, and allowed to stand overnight at room temperature. The reaction mixture was then concentrated under reduced pressure and the residue obtained was dissolved in ether, washed with dilute sodium bicarbonate and then water, and the ether was distilled off. Recrystallization of the residue from isopropyl alcohol afforded white crystals of α-[p-(p'-chlorobenzyloxy)phenoxy]-α-methylpropionic acid nor.-propyl ester having a melting point of 42° to 43.5°C.

Elemental Analysis: as $C_{20}H_{23}O_4Cl$

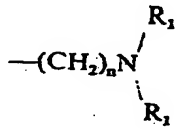
	C	H
Calculated (%)	66.20	6.39
Found (%)	66.37	6.43

WHAT WE CLAIM IS:—

1. Substituted phenoxy-α-methyl-propionic acid derivatives of the following general formula,

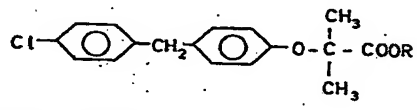


wherein Y stands for —CH_2—, —CH_2O—, —CH_2CH_2— or—CH=CH—, R stands for a hydrogen atom, an alkyl group having 1 to 6 carbon atoms or



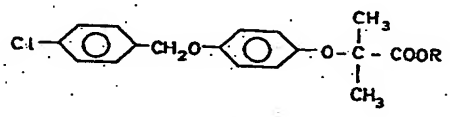
n stands for an integer of 1 to 5 and R_1 stands for an alkyl group having 1 to 6 carbon atoms.

2. Substituted phenoxy-α-methyl-propionic acid derivatives of the following general formula,



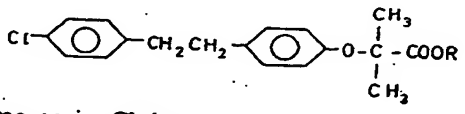
wherein R is the same as in Claim 1.

3. Substituted phenoxy-α-methyl-propionic acid derivatives of the following general formula,



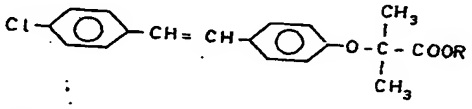
wherein R is the same as in Claim 1.

4. Substituted phenoxy-α-methyl-propionic acid derivatives of the following general formula,



wherein R is the same as in Claim 1.

5. Substituted phenoxy-α-methyl-propionic acid derivatives of the following general formula,



wherein R is the same as in Claim 1.

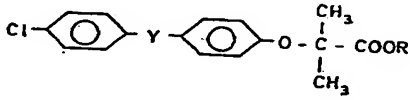
6. Methyl α-[p-(p'-chlorobenzyl)phenoxyl-α-methylpropionate.

7. Methyl α-[p-(p'-chlorobenzyloxy)phenoxyl-α-methylpropionate.

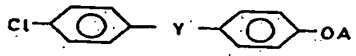
8. Ethyl α-[p-(p'-chlorobenzyl)phenoxyl-α-methylpropionate.

9. Ethyl α-[p-(p'-chlorobenzyloxy)phenoxyl-α-methylpropionate.

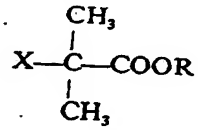
10. A process for producing substituted phenoxy-α-methylpropionic acid derivatives of the following formula,



wherein Y and R are the same as in Claim 1, which comprises reacting a p-substituted phenol or metallic salt thereof of the following formula,



wherein A stands for a hydrogen atom or alkali or alkaline earth metal, with an α-halocarboxylic acid of the following formula,



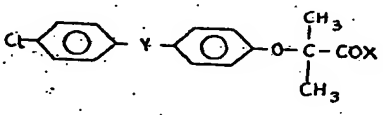
wherein X stands for a halogen atom, and R is the same as in Claim 1.

11. A process as claimed in Claim 10, wherein the p-substituted phenol is p-(p'-chlorobenzyl)phenol or p-(p'-chlorobenzyloxy)phenol.

12. A process as claimed in Claim 10, wherein the α-halocarboxylic acid is an α-bromo-α-methylpropionic acid C_{1-6} alkyl ester.

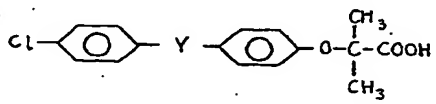
13. A process as claimed in Claim 10, wherein the reaction between the p-substituted phenol or metallic salt thereof and α-halocarboxylic acid is carried out at a temperature ranging from 60°C to 140°C.

14. A process for producing substituted phenoxy-α-methyl-propionic acid derivatives of the following formula,



wherein R_2 stands for an alkyl group having 1 to 6 carbon atoms or

(n and R_1 are the same as in Claim 1), and Y is the same as in Claim 1, which comprises reacting an α-(*p*-substituted phenoxy)-α-methylpropionic acid or reactive derivative therof of the following formula,



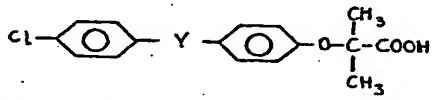
wherein X stands for a hydroxyl group or a halogen, an acyloxy group or an alkoxy group except OR_2, and Y is the same as in Claim 1, with an alcohol of the following formula, R_2OH wherein R_2 is the same as heretofore defined.

15. A process as claimed in Claim 14, wherein the reactive derivative of the α-(*p*-substituted phenoxy)-α-methyl-propionic acid is the acid chloride or anhydride.

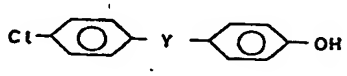
16. A process as claimed in Claim 14, wherein the reaction between the α-(*p*-substituted phenoxy)-α-methylpropionic acid and alcohol is carried out in the presence of *p*-toluenesulfonic acid.

17. A process as claimed in Claim 15, wherein the reaction between the α-(*p*-substituted phenoxy)-α-methylpropionic acid chloride or anhydride and alcohol is carried out in a basic organic solvent or a neutral organic solvent in the presence of a base.

18. A process for producing a substituted phenoxy-α-methylpropionic acid derivative of the following formula,



wherein Y is the same as in Claim 1,
which comprises reacting a *p*-substituted phenol of the following formula,



wherein Y is the same as in Claim 1,
with acetone and a trihalogenomethane in the presence of a base.

19. A process as claimed in Claim 10 and substantially as described in any one of the specific Examples 1—7 hereinbefore set forth.

20. Phenoxy-α-methylpropionic acid derivatives whenever produced by the process claimed in any of claims 10 to 19 or by an obvious chemical equivalent thereof.

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